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Concentration Dependent Physical Behaviour of Superparamagnetic Iron Oxide Nanoparticle Magnetic Resonance Contrast Agents

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Abstract:
Magnetic Resonance Imaging (MRI) is a high resolution diagnostic imaging modality without radiation. Superparamagnetic iron oxide (SPIO)contrast agents are useful to enhance the detection of liver pathology in MR technique.Considering the physiochemical properties of these contrast agents, the particle size plays an important roleas it is a valuable indicator of the efficiency. Therefore, the objective of this study was to evaluate and compare the mean hydrodynamic particle diameter in two types of commonly used superparamagnetic MRI contrast agents, with respect to their concentrations. Measurements onmean hydrodynamicdiameters of Feridex and Resovist were performed in an aqueous medium by Dynamic Light Scattering (DSL) technique. According to the results, specific relationship between the diameters with the concentrations of the considered SPIO was unable to establishin this study. However, a larger surface area was demonstrated for Feridex with comparable to Resovist.

Keywords: *Particle size, Concentration, Dynamic light scattering technique*

1. Introduction

Magnetic Resonance Imaging (MRI) is a rapidly evolving diagnostic tool that provides high resolution anatomical images of soft tissues in the human body without any radiation burden [1, 2]. However, one of the major crucial problem of this approach is, it has relatively low sensitivity compares to the other imaging modalities. Therefore during the precise efficient biomedical-imaging it is essential to improve the signal intensity (SI) to observe the structures at cellular and molecular levels [2, 3].

Generally, the signal intensity (SI) of MR images is governed by proton density, T1 (spin–lattice) and T2 (spin–spin) relaxation times. MR contrast agents (CAs) such as chelates of gadolinium, iron oxide colloids and magnetic compounds have the ability to alter this normal relaxation times, thereby affecting the SI to enhance the visibility of the MR images [1, 4]. According to the manipulation of T1 and T2 relaxation times, in the clinical setting, MR contrast agents can be divided into two categories. Paramagnetic CAs which can produce bright positive signal after an alternation of longitudinal (T1) relaxation times of the neighboring water protons are recognized as positive CAs. On the other hand, superparamagnetic or ferromagnetic contrast agents which can alter transverse (T2/T2*) relaxation times of water protons, appear dark on the MR images are recognized as negative CAs [1, 3, 4].

These superparamagnetic iron oxide (SPIO) MR contrast agents are manufactured after coating the iron oxide crystals which are in nano-sized, with dextran or carboxydextran. The two types of most commonly available superparamagnetic contrast agents in the clinical setting are recognized as Feridex and Resovist [3, 5]. These superparamagnetic iron oxide particles are important in order to characterize the liver pathology and stem cells as they have higher biocompatibility and sensitivity [1, 3, and 4].

When considering the physical properties of the iron oxide CAs, particle size plays a major role on its optimum effects. Generally, the particle size of the contrast agents varies widely, and it influences physiochemical and pharmacokinetic properties, thus clinical application. Among these properties, magnetic and electric properties strongly depend on the particle size of the iron oxide contrast agents [2, 6]. Moreover, the particle sizes also have been shown to be important for cell uptake and in the metabolism of CAs [5].

Thus, CAs should have the proper size and the adequate concentration to produce the optimum effect on the observed signal in MRI with considering other influential factors. Because of this, it is important to measure the particle size distribution of the CAs as it is a significant indicator of the efficiency [4]. Usually the term of hydrodynamic diameter is followed in when describing the particle size of a contrast agent. After monitoring the diffusion characteristics of the particles in a solution, the average hydrodynamic diameter is derived from the Dynamic Light Scattering (DLS) technique [7].

Therefore the objective of this study was to evaluate and compare the mean hydrodynamic particle diameter measurements with respect to their concentrations in two types of most utilizing superparamagnetic contrast agents of Feridex and Resovist.

2. Methods and Materials

In-vitro experiments were performed on Feridex and Resovist with respect to the different concentration levels, to measure the mean hydrodynamic diameter from the dynamic light scattering (DLS) technique. The four concentration levels that used to take the measurements were $0.5x10^{-1}$, $0.5x10^{-2}$, $0.5x10^{-4}$ and $0.5x10^{-6}$mmol/l. Characteristics of these two CAs relevant to this study are shown in Table 1.

DLS experiments were performed using a Microtrac wave particle dynamic light scattering analyzer (Nikkiso, Tokyo, Japan) which can measure the particle sizes ranging from 0.8 - 6500 nm, with a laser diode (3 mW output power) operating at 780 nm. After preparation of the instrument, a few drops of sample were added onto the detector cell until the red bar reaches the green zone on the computer. Then the measurements were taken for each two CA samples separately. In DLS technique, light from a laser diode is coupled to the sample through an optical beam splitter in the probe assembly. The laser is frequency shifted according to the Doppler Effect relative to the velocity of the particles [8]. In this experiment, the temperature was controlled at 25 ^{o}C. First, the histograms which reflect the hydrodynamic diameter with the abundance at each concentration level were derived from the resulted output then the concentration dependent behavior of the CAs conjugate from DLS results.

3. Results and Discussion

The current study was conducted to examine the hydrodynamic particle diameter (volume weighted distribution) of Feridex and Resovist in an aqueous medium as a function of concentration. In addition to that this has allowed the determination of their particle size distribution and surface properties at different concentration levels.

The light scattering patterns of the two types of superparamagnetic contrast agents as a function of concentrations are presented in Figure 1. These results were obtained based on the light scattering property assuming spherical particle geometry with poly-disperse distribution of sizes. The resulted particle sizes are the diameters of hypothetical spheres with their coating materials [4, 7]. When considering the mean values of the hydrodynamic diameters (Figure 1) of the different concentration levels, the highest value was reported at a concentration of 0.5 $x10^{-6}$mol/L for Feridex (749.7 nm) and 0.5 $x10^{-4}$mol/Lfor Resovist (173.9 nm). Because of this, from the obtained results, the diameters were appeared to be not concentration dependent of these contrast agents in this study. However according to the previous studies [5], Feridex is a SPIO colloid which usually demonstrates the hydrodynamic diameter ranging between 120 to 180 nm and Resovistdemonstrates the hydrodynamic diameter ranging between 45 and 60 nm [5]. So these values are not in agree with the current study results (Feridex - 53.9 nm to 749.7 nm and Resovist - 56.3 to173.9 nm) that shows the essentiality of further reviewing of this study.

SPIO nanoparticles have relatively large average particle diameter of around 80 nm and it internalizes into the body for clearance by the mononuclear phagocytic system rapidly. Because of this, clinical applications of SPIO nanoparticles are limited. The development of ultra-small SPIO (USPIO) nanoparticles (<50 nm) is currently attempting to approach these problems [9]. It is important to point out that the concentration levels of $0.5x10^{-1}$mol/Land $0.5x10^{-2}$mol/Lof Feridex and Resovist reported the comparatively less mean diameter (<80nm) which shows the possibility of application in clinical studies. According to Oude Engberink [10] *et al* study results, SPIO particles with around diameter of 150 nm were incorporated into mononuclear cells efficiently than USPIO particles with around diameter of 30 nm. Lager diameter particles were more efficiently internalize and clear from macrophages than smaller particles [11, 12]. The half-life of SPIO particles with a diameter of about 50 nm, is approximately 4–8 min short in the blood due to rapid internalization by the reticuloendothelial system [9].

Table 2 demonstrates the relationship between mean hydrodynamic diameter measurements andStandard Deviation (SD) with the various concentration levels. Standard Deviation (SD) of the resulted graphs is one important measure of the width of the distribution [8]. But no specific relationship could be found between these distributions with the concentrations in this study. However, all the measured contrast agents display the poly-dispersed particle diameter measurements at all the considered concentration levels. Resovist demonstrated the narrowest poly-disperse diameter measurements (27.18 nm) at the concentration level of 0.5 x 10^{-2}mol/L and Feridex demonstrated the widest (1080nm) poly-disperse diameter measurements at the concentration level of $0.5x10^{-6}$mol/L.

Feridex at the concentration level of $0.5x10^{-6}$mol/Land $0.5x10^{-4}$mol/L andResovist at the concentration level of $0.5x10^{-4}$mol/Lwas demonstrated the multi-modal distribution.

Figure 2 demonstrates the comparison between the calculated surface measurement values of Feridex (SPIO) and Resovist (SPIO). This value provides an indication of the specific surface area of the particles at the specific concentration levels assuming spherical particlegeometry. The study has demonstrated a larger surface area of the Feridex with comparable to Resovist [8].

4. Conclusion

According to the results of this study, specific relationship between the hydrodynamic particle diameter distributions with the concentrations of the considered SPIO was unable to establish.

Contrast Agent	Structure	Classification	Target
Feridex(Ferumoxide)	Fe^{2+}/Fe^{3+}(SPIO)	T2 agent	Liver
Resovist (Ferucarbotran)	Fe^{2+} coated with Carboxydextran(SPIO)	T1 and T2 agent	Liver

Table 1: Characteristics of Contrast Agents [13]

Concentration (mmol/l)	Feridex		Resovist	
	Mean(nm)	SD(nm)	Mean(nm)	SD(nm)
$0.5x10^{-1}$	53.9	43	56.3	28.24
$0.5x10^{-2}$	59.8	48.85	58.78	27.18
$0.5x10^{-4}$	101.2	33.06	173.9	142.5
$0.5x10^{-6}$	749.7	1080	73.05	51.65

Table 2: Mean Diameter Distribution and Standard Deviation in two types of SPIO at Different Concentrations

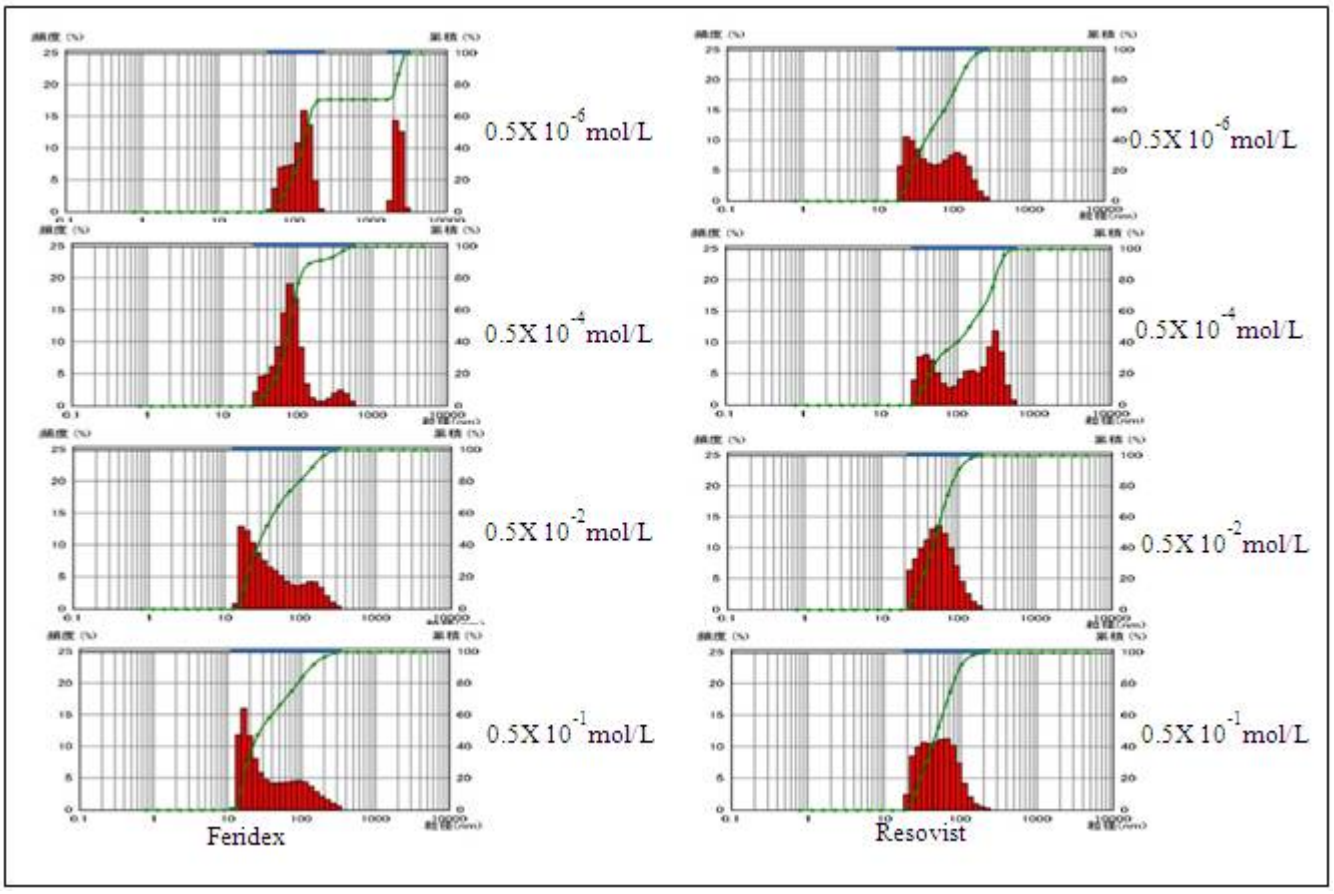

Figure 1: Light scattering measurements of Feridex and Resovist

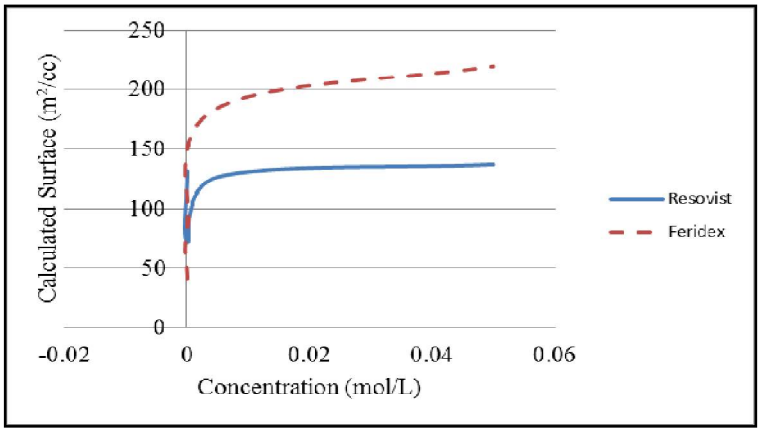

Figure 2: Comparison of the calculated surface measurement values of Feridex and Resovist

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